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Chronic Pure Red Cell Aplasia Caused by Parvovirus B19 in AIDS: Use of Intravenous Immunoglobulin—A Report of Eight Patients

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The optimal management of chronic pure red cell aplasia caused by parvovirus B19 (B19-PRCA) in patients with AIDS is unclear. Our purpose was to determine the effects of intravenous immunoglobulin (IVIg) in the treatment of B19-PRCA in patients with AIDS. The patients were eight adults with AIDS admitted during the period 1993–1997. A diagnosis of B19-PRCA was made if all the following criteria were met: 1. Bone marrow biopsy finding of pure red cell aplasia; 2. Detection of parvovirus B19 DNA in serum; and 3. No alternative explanation for PRCA. Initial (induction) therapy was with IVIg 1 g/kg daily for 1–2 days. Relapses were treated with IVIg 1 g/kg for 2 days. Maintenance therapy with IVIg 0.4–1.0 g/kg q 4 weeks was given to those patients who developed a second or subsequent relapse. The patients were followed for a mean of 27 months (range 8–38 months). All patients responded to initial therapy with IVIg. Six patients with CD4 counts <80 cells/mm^3 relapsed. The response was short lived in two patients with a CD4 count <80 cells/mm^3 who were given a single infusion of IVIg 1 g/kg as initial therapy. Four patients were given regular maintenance IVIg therapy following a second or subsequent relapse and remain in remission. Two patients whose CD4 counts were >300 cells/mm^3 remain in continuous unmaintained remission from B19-PRCA for over 8 and 11 months, respectively, following induction therapy with IVIg. AIDS patients with B19-PRCA respond well to therapy with IVIg 2 g/kg given over 2 days. Most patients with CD4 counts of ≤80 cells/mm^3 suffer relapse within six months necessitating retreatment with IVIg; maintenance therapy with IVIg 0.4 g/kg q 4 weeks is effective in preventing relapse of B19-PRCA, and may be cost effective. Routine maintenance therapy is probably not indicated in patients with CD4 counts over 300 cells/mm^3. Prospective studies are needed to confirm these findings. Am. J. Hematol. 61:16–20, 1999. © 1999 Wiley-Liss, Inc.

Key words: AIDS; parvovirus B19; red cell aplasia; anemia

INTRODUCTION

Parvovirus B19 (B19) is an important and treatable cause of severe anemia in patients with AIDS [1,2]. Following B19 infection, the defective immune response in these patients causes persistent viremia and chronic pure red cell aplasia (B19-PRCA).

Intravenous immunoglobulin (IVIg) is a good source of neutralizing antibodies against the virus and is an effective treatment for B19-PRCA. Most authors have reported treating patients with IVIg 0.4 g/kg daily for 5–10 days, which has resulted in brisk reticulocytosis and a rise in hemoglobin (Hb) [3]. However, relapses are common and the value of maintenance therapy with IVIg in preventing relapses has not been well studied. We report on our experience with IVIg 1 g/kg for 1–2 days in the initial (induction) therapy of B19-PRCA in eight adult AIDS patients followed for a mean of 27 months (range 8–38 months) and the use of maintenance IVIg in the management of the patients at relapse.

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TABLE I. Anemia Due to B19 Infection in AIDS: Clinical and Laboratory Data in Eight Patients at Diagnosis*

Patient no.	Age	Sex	ZDV	Hb g/dl	MCV fl	Retic %	WBC $\times 10^9$/l	Plt $\times 10^9$/l	PRCA	Serum iron μg/dl	Sat %
1	36	M	Yes	4.3	100	0	4.2	364	Yes	247	74
2	33	M	Yes	4.7	89	0	12.9	567	Yes	199	80
3	36	M	Yes	3.2	91	0	9.8	606	Yes	ND	ND
4	29	M	No	5.6	84	0	1.4	158	ER	ND	ND
5	40	M	No	8.3[a]	86	0	6.4	439	Yes	227	79
6	32	M	Yes	2.9	93	0	3.5	419	Yes	171	66
7	45	M	No	3.8[b]	88	0	2.3	292	Yes	247	77
8	25	F	No	4.2	81	0	2.8	335	Yes	ND	ND

*ZDV, zidovudine use; Hb, hemoglobin; MCV, mean corpuscular volume; Retic, reticulocytes; WBC, white blood cell count; Plt, platelet count; PRCA, pure red cell aplasia; Sat, transferrin iron saturation; ER, bone marrow showing evidence of early recovery from PRCA (see text); ND, not done.
[a]Value after 4 units packed erythrocyte transfusion.
[b]Hb value at the time of bone marrow biopsy showing pure red cell aplasia (see Results section).

PATIENTS AND METHODS

The patients were adults with AIDS admitted to Cook County Hospital during the period 1993–1997 and referred to Hematology service because of anemia. All patients were evaluated and followed by one of the authors.

The history, medications, and physical findings were recorded. A complete blood count, reticulocyte count, $CD4^+$ T-lymphocyte (CD4) count, serum creatinine, chest radiograph, serum total bilirubin, a direct antiglobulin test, test for IgM and IgG antibodies to B19, serum test for B19 DNA, and a bone marrow biopsy were obtained in all patients. In five patients the serum iron and transferrin level were determined.

IgM and IgG antibodies to B19 were determined by an indirect immunofluorescence test using a commercial kit (Incstar Corporation, Stillwater, MN). Blood was tested for B19 DNA by polymerase chain reaction (PCR) amplification (Specialty Laboratories, Santa Monica, CA).

The diagnosis of PRCA required the virtual absence of erythroid precursors except for occasional giant or normal appearing proerythroblasts in an otherwise normal marrow. The marrow was considered to show evidence of early recovery of erythropoiesis if there were abundant normal proerythroblasts, but no erythroid precursors beyond the stage of the proerythroblast.

The anemia was considered to be due to B19 infection if all of the following criteria were met: 1. Absence of reticulocytes in blood; 2. Bone marrow biopsy finding of PRCA; 3. Detection of B19 DNA in serum; and 4. Absence of an alternative explanation for the anemia based on findings at the time of initial evaluation or during follow-up. A relapse of PRCA despite discontinuation of zidovudine, or resolution of anemia while on the zidovudine was taken as evidence against a diagnosis of zidovudine-related anemia. A bone marrow biopsy finding of "early recovery of erythropoiesis" was also considered acceptable as a diagnostic criterion for B19-related anemia, if the marrow sample was obtained 2–3 days after transfusion of fresh packed erythrocytes.

Response to IVIg was defined as a rise in the blood Hb concentration of >3 g/dl not due to packed erythrocyte transfusion, occurring within 4 weeks of treatment with IVIg. Relapse was defined as an otherwise unexplained drop in the blood Hb concentration of >3 g/dl, together with absent blood reticulocytes. If a patient relapsed, a bone marrow biopsy was performed to identify red cell aplasia. The duration of follow-up was calculated from the time of the initial therapy with IVIg. The time to relapse was calculated from the time when response was achieved. Relapses from B19-related anemia were treated with IVIg 1 g/kg for 2 days.

RESULTS

All patients contracted HIV infection through unprotected sex. The clinical and laboratory features of these patients are shown in Table I. The IgM and IgG antibodies to B19 were negative in all patients at the time of their initial diagnosis with B19-PRCA. The IgG antibodies to B19 were intermittently positive in some patients during follow-up and this was attributed to the passive acquisition of the antibody through Ig infusion. The direct antiglobulin test, serum creatinine, and chest radiography were normal or negative in all patients.

All patients presented with nonspecific symptoms of anemia and denied having fever, diarrhea, joint pains, or skin rash. Two patients presented following an episode of syncope. Three patients were transfusion dependent for periods ranging from 6 weeks to 36 months and had received a total of 6, 15, and 65 units of packed erythrocytes, respectively, prior to the diagnosis of B19-related anemia. The clinical examination showed normal body temperature and marked pallor in all patients, mild splenomegaly in two patients, and oropharyngeal thrush in two others. Patients 2 and 6 had been HIV-1 seropositive for 6 and 10 years respectively and were in excellent health until their admission for B19-related anemia.

In two patients (patients 3 and 7) with pretransfusion

TABLE II. Chronic B19-PRCA in Patients With AIDS: Results of IVIg Therapy*

Patient no.	CD4 cells/mm^3	Ig Induction dose × days	F/U mo	R1 mo	R2 mo	R3 mo	Max Hb g/dl	MIg dose, frequency	Remarks
1	27	1 g/kg × 2d	38	8	8	7[a]	13.1	0.4 g/kg, q 4 weeks	[a]MIg during R4
2	48	1 g/kg × 2d	36	5	4	7+	14.8	1.0 g/kg, q 4 weeks	MIg during R3
3	36	1 g/kg × 2 d	35	6	8	5+[b]	12.8	0.4 g/kg, q 4 weeks	MIg during R3
4	5	1 g/kg × 2 d	8	7	1		12.0	None	Died
5	412	1 g/kg × 2 d	9	8+			12.8	None	Alive, well
6[c]	63	1 g/kg × 1 d	22	<3	5	7	14.3	0.4 g/kg, q 4 weeks	MIg during R3[d]
7	8	1 g/kg × 1 d	28	3	4	14+	14.8	0.4 g/kg, q 4 weeks	MIg during R3
8	316	1 g/kg × 1 d	37	11+[e]			11.1	None	

*CD4, = $CD4^+$ T-lymphocyte count; Ig, immunoglobulin; F/U, duration of follow-up; R1, R2, R3, R4, duration of first, second, third, and fourth remission from anemia following Ig therapy; Max Hb, maximal hemoglobin after Ig therapy; MIg, maintenance immunoglobulin therapy.
[a]R4 duration 8+ months.
[b]Subsequent follow-up has been irregular with recurrent anemia responding to reinduction with IVIg.
[c]This patient has been reported elsewhere [4].
[d]Received only two doses of MIg therapy.
[e]Developed anemia of chronic disorder due to multiple infections, and refused repeat marrow biopsy.

Hb values of 3.2 and 1.6 g/dl respectively, blood reticulocytes were absent and the bone marrow showed an unexpected finding of erythroid hyperplasia. They had been transfused with 4–6 units of packed erythrocytes, 2–3 days prior to the bone marrow biopsy. Neither patient was treated with IVIg. Both were readmitted with symptomatic anemia within 2 months of discharge and a repeat bone marrow biopsy showed PRCA with giant proerythroblasts.

Table II shows the response to IVIg in our patients. The patients were followed for a mean of 27 months (range 8–38 months). Five patients given initial induction therapy with 2 g/kg IVIg responded with remissions from anemia lasting 5–8 months (mean 6.9 months). Three patients were given induction therapy with IVIg 1 g/kg. Of these, two patients with CD4 counts of <80 cells/mm^3 had a short-lived remission of 3 months or less. The third patient (patient 8) whose CD4 count was 316 cells/cmm^3 has remained in remission for about 11 months; she has subsequently developed anemia (Hb 8–9 g/dl) in association with disseminated infection with *H. capsulatum* and *Mycobacterium avium* complex (MAC) and refused consent for a bone marrow biopsy. Patient 2 developed disseminated MAC and *Cytomegalovirus* (CMV) infection and became transfusion dependent during the last 8 months of his life despite monthly IVIg infusions; he refused consent for a repeat bone marrow biopsy. The spleen was no longer palpable after Ig therapy in the two patients who had splenomegaly at presentation.

Four patients received regular monthly maintenance therapy with IVIg 0.4–1 g/kg (Table II). Two patients (patients 1 and 7) remain in remission from anemia for 8 and 14 months, respectively . Maintenance IVIg therapy was discontinued in patient 3 because of poor compliance; subsequently he has had recurrent anemia that has responded to reinduction with 2g/kg IVIg on three occasions during an 8-month period. The fourth patient developed an anemia of chronic disease due to disseminated MAC and CMV infection refractory to therapy.

The serum was positive for B19 DNA in four patients while they were in remission and receiving maintenance IVIg therapy. The serum of patient 1 tested positive for B19 DNA during his fourth remission while receiving maintenance IVIg therapy. It had been tested monthly for B19 DNA during the preceding 3 months and found to be negative. A total of 12 bone marrow biopsies were done in four patients during their follow-up for suspected relapse. Eleven of these showed PRCA; the patient with the nondiagnostic bone marrow biopsy had been on monthly maintenance Ig therapy and was diagnosed with anemia of chronic disease due to disseminated MAC infection.

A review of the English language literature showed 12 reports describing a total of 21 HIV-infected patients with B19 PRCA treated with IVIg (Table III).

DISCUSSION

The clinicopathological features of PRCA due to B19 infection in our patients with AIDS were fairly consistent. The patients had symptoms attributable to severe anemia and all but two patients had a history of prior AIDS-defining illnesses. They were afebrile and their examination was generally unremarkable except for marked pallor.

The hematological findings in our patients consisted of severe anemia, normal mean corpuscular volume in all but two patients, and absent blood reticulocytes. The serum iron and transferrin iron saturation were elevated in all five patients in whom they were measured. These findings, together with PRCA (or evidence of early recovery from PRCA), and the detection of B19 DNA in the serum established the diagnosis of B19-PRCA in our patients.

TABLE III. Results of IVIg therapy in HIV-Infected Patients With Anemia Due to B19 Infection: Literature Review*

Year	Author, reference	n	CD4	Ig induction	F/U	Relapse	R1	Ig maintenance
1990	Frickhofen et al. [1]	6	NR	0.4 g/kg × 5 days	13 months	No	13 months	None
			80	0.4 g/kg × 10 days	8 months	Yes	6 months	None
			80	0.4 g/kg × 5 days	8 months	Yes	3 months	None
			360	0.4 g/kg × 5 days	7 months	No	7 months	None
			330	0.4 g/kg × 10 days	7 months	No	7 months	None
			60	0.4 g/kg × 5 days	>7 weeks	Yes	7 weeks	None
1990	Bowman et al. [6]	1	NR	0.7 g/kg × 3 days	3 months[a]	—	—	—
1990	Mitchell et al. [7][b]	1	NR	0.3 g/kg × 8 days	11 months	Yes	5 months	None
1992	Gottlieb et al. [8]	1	35	1.0 kg/d × 2 days	18 weeks	Yes	10 weeks	None
1992	Mitsuyasu et al. [9]	1	80	0.4 g/kg × 5 days	6 months	Yes	4–6 months	None
1992	Taillan et al. [10]	1	NR	0.4 g/kg × 3 days	4 months	No	4 months+	None
1994	Zuckermann et al. [11]	3	NR	0.4 g/kg × 5 days	10 months	NR	NR	None
				0.4 g/kg × 5 days	5 months	NR	NR	None
				0.4 g/kg × 5 days	10 months	NR	NR	None
1995	Chernak et al. [12]	1	49	0.4 g/kg × 5 days	>6 months	NR	6 months	None
1995	Ramratnam et al. [13]	1	6	0.4 g/kg × 5 days	51 months	Yes	7 weeks	0.4–1.1 g/kg q 2–3 weeks
1996	Fuller et al. [14]	1	22	0.4 g/kg × 5 days	29 months	Yes	6 months	30 g/d q 4 weeks
1997	Abkowitch et al. [2]	4	80	0.4 g/kg × 5 days	3–4 years	No	3–4 years	None
			36	0.4 g/kg × 5 days	3–4 years	No	3–4 years	None
			10	0.4 g/kg × 5 days	NR	Yes	NR	None
			50	0.4 g/kg × 5 days	11 months	NR	NR	None

*n, number of patients; CD4, $CD4^+$ T-lymphocyte count/mm^3; Ig, immunoglobulin; F/U, total duration of follow-up; R1, duration of first remission from anemia following Ig therapy; NR, not reported.

[a]Patient did not respond to Ig therapy and died of disseminated *Mycobacterium avium* complex infection.

[b]This patient has also been reported by Chrystie et al. [15].

The unexpected finding of erythroid hyperplasia in patients 3 and 7 at the time of their initial evaluation for anemia is of interest. It is possible that the presence of B19-specific antibodies in the plasma contained in the packed erythrocyte transfusion may have resulted in virus neutralization and resumption of erythropoiesis in these patients [5].

Most HIV-infected patients with B19-PRCA described in the literature have been treated with IVIg 0.4 g/kg for 5–10 days with excellent results. The lack of response to IVIg has been reported only once in a patient who died soon after diagnosis, of disseminated MAC infection refractory to therapy [6]. The schedule of IVIg administration using 1–2 g/kg given over 1–2 days has been reported infrequently [8]. Most authors report using a dose of 2 g/kg given over 5 days. Our patients' response to initial induction therapy with IVIg 2 g/kg for 2 days is comparable to that reported by others using IVIg 0.4 g/kg for 5–10 days (Table III) and may be more cost effective.

The majority of patients with AIDS and B19-PRCA reported to date have relapsed (Table III). Of the patients in whom the CD4 counts were reported, seven of the nine with CD4 counts $\leq$80 cells/mm^3 had relapsed within 6 months (range 7 weeks to 6 months) of induction IVIg therapy; the other two patients have remained in remission for 3–4 years [2]. Maintenance IVIg therapy following a relapse has been reported in two patients [13,14] with CD4 counts of 6 and 22 cells/mm^3, respectively, and appears to have prevented subsequent relapses in both.

All six of our patients with CD4 counts <80 cells/mm^3 relapsed with blood Hb concentrations of 3.8 to 6.6 g/dl at relapse and required up to 4 units of packed erythrocyte transfusion. In four patients given initial therapy with 2 g/kg IVIg the remissions lasted 5–8 months; remissions lasted 3 months or less in the remaining two patients who received an induction IVIg dose of 1g/kg. The definition of relapse used in our study (an unexplained drop in the Hb of >3 g/dl) may have resulted in an overestimate of the duration of remission. It is possible that more frequent follow-ups may have helped in detecting relapse sooner in our patients.

Almost all patients with B19-PRCA and CD4 counts of less than 100 cells/mm^3 may be expected to relapse, generally within 6 months of initial therapy. Relapses respond to reinduction therapy with 2g/kg IVIg. The role of maintenance IVIg therapy following initial IVIg therapy in preventing relapses has not been prospectively investigated. A policy of routine maintenance therapy with IVIg 0.4 g/kg q 4 weeks in our patients with CD4 counts $\leq$80 cells may have resulted in prevention of relapse and decreased the requirement of packed erythrocytes transfusion without increasing the total dose of IVIg used. This approach to maintenance IVIg therapy appears to be cost effective.

The risk of early relapse in patients with B19-PRCA who have CD4 counts >300 cells/mm^3 is probably low. Patient 8 whose CD4 count was 316/mm^3 had a remission lasting >11 months following initial therapy with IVIg 1 g/kg. Frickhofen et al. [1] reported on two patients with CD4 counts >300 cells/mm^3 both of whom re-

mained in remission without maintenance IVIg for >7 months. The dose of IVIg in the initial therapy of this group of patients with CD4 counts of >300 cells/mm^3 requires investigation.

IVIg treatment markedly decreases the virus load but the virus remains detectable by the sensitive PCR amplification test during hematological remission [1,2,16,17]. DNA dot-blot hybridization test of patient sera has been proposed as having a greater specificity than the PCR assay for the diagnosis of B19-PRCA at presentation in HIV-infected patients [2]. The utility of this test during follow-up of these patients after IVIg treatment needs investigation. In patient 1 three consecutive monthly serum samples were negative for B19 DNA and would have resulted in a decision to discontinue IVIg maintenance therapy except for a subsequent serum sample that tested positive a month later.

Induction therapy with IVIg 2 g/kg given over 2 days is effective for B19-PRCA in patients with AIDS. Routine maintenance therapy with IVIg 0.4 g/kg q 4 weeks should be considered in all patients with CD4 counts of $\leq$80 cells/mm^3. Routine maintenance IVIg therapy may not be needed in patients with AIDS and B19-PRCA whose CD4 counts are over 300 cells/mm^3. Prospective studies are needed to confirm our findings.

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